residues of about 87-108 (SEQ ID NO:1) or [and] about 59-80 (SEQ ID NO:2) of hTNFα.

36. (Amended) A method of Claim 34 wherein the chimeric antibody [binds to the epitope of] competitively inhibits binding of TNFα to monoclonal antibody cA2.

37. (Amended) A method of Claim 36 wherein the chimeric antibody is monoclonal antibody cA2.

REMARKS

Applicants' invention is based on the surprising discovery that inhibition of the biological activity of TNFα reduces fibrinogen levels in an individual, which thus, results in the direct treatment of thrombosis in the individual. The amendments to the claims are made to more clearly define the invention. No new matter is introduced by the amendments. The Office Action will now be addressed under separate headings.

Restriction Requirement

The Examiner maintains the restriction requirement. Applicants are filing concurrently herewith a Petition under 37 C.F.R. § 1.144. Reconsideration of the restriction requirement for the reasons set forth therein is respectfully requested.

Drawings

Applicants acknowledge that formal drawings will be filed no later than in response to the Notice of Allowance.

Cited U.S. Applications

The status of the U.S. applications cited in the subject application have been updated.

Rejection of Claims 8-15 Under 35 U.S.C. § 112, Second Paragraph

Claims 8-15 have been rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

As amended, the claims indicated include the following changes, made in response to the specific rejections made by the Examiner:

a) Claims 8 and 9 are rejected to as indefinite in the recitation of "fragments thereof" because "the nature of the claimed fragments is unclear."

Claims 8 and 9 have been amended to recite "antigen-binding fragments thereof." Support for this amendment is found in the specification, for example, at page 7, lines 29-30. The person of skill in the art would not find the phrase to be indefinite.

b) Claims 9 and 12 are rejected to as vague and indefinite in the recitation of "chimeric" because the "metes and bounds of the claims are unclear." Applicants respectfully disagree with this assessment.

Applicants disclose in the specification that the term "chimeric antibody" includes monovalent, divalent and polyvalent immunoglobulins (see, e.g., page 10, lines 12-13). A monovalent chimeric antibody is defined to be a dimer (HL) formed by a chimeric H chain associated through disulfide bridges with a chimeric L chain (see, e.g., page 10, lines 13-16). A divalent chimeric antibody is defined to be a tetramer (H_2L_2) formed by two HL dimers associated through at least one disulfide bridge (see, e.g., page 10, lines 16-18). A polyvalent chimeric antibody is defined to be produced, for example, by employing a

CH region that aggregates (e.g., from an IgM H chain or μ chain) (see, e.g., page 10, lines 18-21).

A chimeric H chain is defined as comprising an antigen binding region derived from the H chain of a non-human antibody specific for TNF, which is linked to at least a portion of a human H chain C region (CH) (see, e.g., page 10, lines 23-27). A chimeric L chain is defined as comprising an antigen binding region derived from the L chain of a non-human antibody specific for TNF, linked to at least a portion of a human L chain region (see, e.g., page 10, lines 27-30).

Applicants disclose that anti-TNF chimeric antibodies can comprise, for example, two light chains and two heavy chains, each of the chains comprising at least part of a human constant region and at least part of a variable region of non-human origin having specificity to human TNF (see, e.g., page 11, lines 16-23). Specific examples of anti-TNF chimeric antibodies are provided as well. Thus, it is respectfully submitted that the term "chimeric antibody" is definite and the metes and bounds of the claims are clear, when read in light of the specification.

c) Claims 11 and 14 are rejected to as vague and indefinite in the recitation of "binds to the epitope of" because is unclear whether "the claimed antibody binds to the same antigenic epitope that the A2 and cA2 antibodies bind" or "to an epitope formed by the A2 or cA2 antibody itself".

Claims 11 and 14 have been amended to delete the phrase "binds to the epitope of" and to recite that the antibody competitively inhibits binding of TNF to monoclonal antibody A2 or cA2. Support for this amendment is found in the specification, for example, at page 8, lines 11-13; and page 12, lines 7-10. The person of skill in the art would not find the phrase to be indefinite.

d) Claim 11 is rejected to as vague and indefinite in the recitation of "A2" because the term is "a laboratory recitation

and not an art accepted term." Applicants respectfully disagree with this rejection.

As stated in Applicants' specification (see, e.g., page 8, lines 15-20), murine monoclonal antibody A2 has been defined and described in detail in, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272). This reference provides significant description of the properties and methods for producing murine monoclonal antibody A2. Thus, it is respectfully submitted that the term "A2" is definite. There is nothing inappropriate in employing a laboratory designation in a claim and the Examiner has not provided any basis for a contrary conclusion. Indeed, an Applicant is permitted to be his own lexicographer.

e) Claims 14 and 15 are rejected to as vague and indefinite in the recitation of "cA2" because the term is "a laboratory recitation and not an art accepted term." Applicants respectfully disagree with this rejection.

As stated in Applicants' specification (see, e.g., page 12, lines 12-17), chimeric monoclonal antibody cA2 has been defined and described in detail in, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272). This reference provides significant description of the properties and methods for producing chimeric monoclonal antibody cA2. Thus, it is respectfully submitted that the term "cA2" is definite. Again, there is nothing inappropriate in employing a laboratory designation in a claim. Indeed, an Applicant is permitted to be his own lexicographer.

f) Claims 10 and 13 are rejected to as vague and indefinite in the recitation of "binds to one or more amino acid residues of TNFα selected from the group consisting of about 87-108 and about 59-80" because "it is unclear how the amino acid residue is selected from groups consisting of two different peptides."

Claims 10 and 13 have been amended to recite that the antibody binds to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNF. Support for this amendment is found in the specification, for example, at page 14, lines 13-15. The person of skill in the art would not find the phrase to be indefinite.

g) Claims 6 and 7 are rejected to as vague and indefinite in the recitation of "thrombotic disorder" because "the metes and bounds of disorders encompassed by 'thrombotic' is unclear." Applicants respectfully disagree with this assessment.

As defined in the specification, a "thrombotic disorder" is a condition where thrombosis is a pathogenic component (see, e.g., page 6, lines 3-4). Thus, a clear definition that would be readily understood by the skilled artisan has been provided in the specification. Applicants disclose that a thrombotic disorder includes thromboembolic disorders, ischemic events, stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis (see specification, e.g., page 6, lines 5-8). Thus, the specification provides examples of what is envisioned by the term. Thus, it is respectfully submitted that the term "thrombotic disorder" is definite.

Notwithstanding the above, Claim 6 has been amended to delete "thrombotic disorder" and recite thrombosis. Support for this amendment is found in the specification, for example, at page 6, lines 19-20. Claim 7 has been cancelled.

Objection to the Specification and Rejection of Claims 11 and 14-15 Under 35 U.S.C. § 112, First Paragraph

The Examiner has objected to the specification and rejected Claims 11 and 14-15 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification fails to provide evidence that cell lines expressing A2 and cA2 are known and readily available to the public or deposited. Applicants respectfully disagree with this assessment.

Claims 11 and 14 have been amended to recite treatment with an antibody which competitively inhibits binding of TNFα to monoclonal antibody A2 and monoclonal antibody cA2, respectively, to further clarify the invention sought to be claimed. Claim 15 recites treatment with monoclonal antibody cA2.

The Court of Appeals for the Federal Circuit has stated that:

> No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988).

The subject application, for example, at page 8, lines 15-20 and page 12, lines 12-17, incorporates by reference information on A2 and cA2 to other U.S. patent applications not listed as priority documents. In particular, the subject application incorporates by reference information on A2 and cA2 described in U.S. Application 08/192,093 (filed February 4, 1994), U.S. Application No. 08/192,102 (filed February 4, 1994) (now U.S. Patent No. 5,656,272; issued August 12, 1997), U.S. Application No. 08/192,861 (filed February 4, 1994) and U.S. Application No. 08/324,799 (filed October 18, 1994; allowed May 28, 1997) (see specification, e.g., page 8, lines 15-20 and page 12, lines 12-17).

The referenced U.S. patent applications disclose the cloning and recombinant expression of the A2 and cA2 monoclonal antibodies, including the sequencing of the light and heavy chain variable regions. The referenced patent applications also provide significant description of the properties (e.g., glycosylation, epitopic specificity and affinity) of the chimeric anti-TNFα antibody cA2 and the murine anti-TNFα antibody A2. With this information, screening of antibodies which have the same or similar properties is straightforward to one skilled in the art.

Thus, given the guidance presented in the incorporated patent and related applications, it would be a routine matter for one skilled in the art to produce the monoclonal antibodies A2 and cA2 and antibodies chemically and structurally similar to the A2 and cA2 antibodies for use in the claimed invention. Therefore, the A2 and cA2 antibodies are enabled by the present specification, in view of the incorporation by reference to these referenced applications and a deposit is not required.

In view of the foregoing amendments and discussion, withdrawal of this objection to the specification and rejection of Claims 11 and 14-15 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Objection to the Specification and Rejection of Claims 6-15 Under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 6-15 rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an adequate written description of the invention or enable the scope of the claims. Each specific rejection is addressed in the order presented by the Examiner:

a) Claims 6 and 7 are rejected on the grounds that (1) it would require undue experimentation for one skilled in the art to identify TNF antagonists effective in the claimed methods; (2) it would be unpredictable that a particular TNF antagonist would be effective in the claimed treatment method when administered by the means disclosed in the specification; and (3) one skilled in the art could not practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success. Applicants respectfully disagree.

As defined in the specification, TNF antagonists decrease, block, inhibit, abrogate or interfere with TNF activity *in vivo*. (see, e.g., page 7, lines 6-9). Applicants disclose that such TNF antagonists include anti-TNF antibodies and receptor

molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signalling (see specification, e.g., page 7, lines 9-25). Specific examples are provided as well. As the Examiner is undoubtedly aware, there are numerous TNF antagonists which are known in the art. As the Examiner states, the specification exemplifies methods that comprise administration of anti-TNF antibodies (Office Action, page 7). Since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNF), it is expected, based upon scientific reasoning, that the claimed invention works in the same manner using other TNF antagonists.

Thus, armed with Applicants' teachings, it would not require undue experimentation for one skilled in the art to practice the claimed invention with a reasonable expectation of success. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

b) Claims 6-15 are rejected on the grounds that one skilled in the art could not practice the claimed invention with a reasonable expectation of success because (1) no *in vitro* or *in vivo* evidence is presented which shows that the administration of anti-TNF antibodies is effective in the treatment of thrombotic disorders; and (2) it is not art accepted that the administration of an agent that reduces fibrinogen levels will be an effective clinical method for the treatment of thrombotic disorders. Applicants respectfully disagree with this assessment.

Claims 6 and 8-15, as amended, relate to methods of treating or preventing thrombosis in an individual comprising administering a therapeutically effective amount of a TNF antagonist to the individual. Claim 7 has been cancelled.

To be enabling under 35 U.S.C. § 112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 27 U.S.P.Q.2d 1510, 1513 (Fed.

Cir. 1993). The Court of Appeals for the Federal Circuit has stated that "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." Id.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. Id.

The specification teaches that thrombosis can be treated or prevented in an individual by administering a TNF antagonist to the individual in therapeutically effective amounts (see, e.g., page 6, lines 19-20). Examples of TNF antagonists that can be used in the claimed invention are provided in the specification, for example, at page 7, line 9 to page 29, line 7. Guidelines for route of administration and dosages are provided in the specification, for example, at page 29, line 9 to page 32, line 4.

The Examiner acknowledges that the specification demonstrates that the administration of anti-TNFα antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to normal and that inhibition of the biological activity of TNFα reduces fibrinogen and platelet levels in individuals with active rheumatoid arthritis. Since platelets and fibrinogen play integral roles in thrombosis, this evidence would satisfy one skilled in the art on the effective filing date of the application that anti-TNF antibodies would likely be effective in the treatment of thrombosis. In addition, since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNFα), it is expected, based upon scientific reasoning, that the claimed methods work in the same manner using other TNFα antagonists.

Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to practice the claimed invention without undue experimentation and with a reasonable expectation of success. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

c) Claim 6 is rejected on the grounds that no definition for "thrombotic disorder" is provided in the specification and that lacking such guidance, one skilled in the art cannot identify "thrombotic disorders" and cannot practice the invention commensurate with the scope of the claims. Applicants respectfully disagree with this assessment.

As discussed above, "thrombotic disorder" is defined in the specification as a condition where thrombosis is a pathogenic component (see, e.g., page 6, lines 3-4). Thus, a clear definition that would be readily understood by the skilled artisan has been provided in the specification. Applicants disclose that a thrombotic disorder includes thromboembolic disorders, ischemic events, stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis (see specification, e.g., page 6, lines 5-8). Thus, the specification provides examples of what is envisioned by the term.

Notwithstanding the above, Claim 6 has been amended to delete "thrombotic disorder" and recite thrombosis. Claim 7 has been cancelled.

As discussed above, the guidance provided in the specification is sufficient to teach the skilled artisan how to practice the claimed invention without undue experimentation.

The Examiner's discussion of Meade is noted but is not understood. Meade teaches that fibrinogen contributes to pathological and clinical manifestations of ischaemic heart disease and that high fibrinogen levels are thrombogenic. These teachings support the conclusions drawn in Applicants' specification.

Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

d) Claims 8 and 9 are rejected on the grounds that "[a]n almost limitless variety of 'fragments' can be prepared from anti-tumor necrosis factor antibodies and by a wide range of methods". The Examiner states that it would require undue experimentation for one skilled in the art to practice the invention commensurate with the scope of the claims. Applicants respectfully disagree with this assessment.

Claims 8 and 9 have been amended to recite antigen-binding fragments.

It is noted that the Examiner acknowledges that the specification provides "guidance for the preparation and identification of 'fragments thereof' for use in the claimed method of treatment." The specification also provides methods for determining monoclonal antibody specificity and affinity (see, e.g., page 13, lines 1-12). Thus, armed with Applicants' teachings, it would be a routine matter for one skilled in the art to practice the claimed invention. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

e) Claims 10 and 13 are rejected on the grounds that antibodies that bind to one or more amino acid residues of TNFα selected from the group consisting of about 87-108 and about 59-80 can be interpreted to antibodies that bind to a single amino acid residue selected from the region of the TNF protein determined by amino acids 87-108 or 59-80. The Examiner states that the specification provides no guidance for the preparation of such an antibody.

Claims 10 and 13 have been amended to recite that the antibodies bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα.

The specification provides methods for producing antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα. Specifically, the specification provides methods for producing anti-TNF antibodies and for determining the epitopic specificity of these antibodies (see, e.g., page 17, lines 11-18, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272)).

Thus, given the guidance presented in the specification, it would be a routine matter for one skilled in the art to produce and identify antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of Claims 6 and 7 Under 35 U.S.C. § 102(e)

Claims 6 and 7 have been rejected under 35 U.S.C. § 102(e) as being unpatentable over U.S. Patent No. 5,547,979 ('979).

The Court of Appeals for the Federal Circuit has stated that "[u]nder 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986) (citations omitted).

Claim 6, as amended, is drawn to a method of treating or preventing thrombosis in an individual. Claim 7 has been cancelled.

The '979 patent discloses a method of treating tissue injury in disorders such as, reperfusion injury, myocardial infarction, stroke or circulatory shock in a mammal comprising administering to the mammal an effective TNF inhibiting amount of a compound of Formula I (disclosed in the reference) (see col. 6, l. 20-25). That is, the patent suggests treatment of the inflammation "mediated or exacerbated by TNF production" which results from these events (see the Abstract).

Applicants' invention rests in their discovery that inhibiting TNFα results in a decrease in fibrinogen levels in an

individual which, thus, results in the direct treatment of the thrombosis in the individual. The method of Claim 6, as amended, differs from the method of the '979 patent in the disorder to be treated (i.e., thrombosis versus tissue injury due to reperfusion injury, myocardial infarction, stroke or circulatory shock). Therefore, Claim 6, as amended, is not anticipated by the '979 patent since it does not relate to treating the tissue injury of the disorder.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 102(e) are respectfully requested.

Rejection of Claims 6-9 Under 35 U.S.C. § 102(e)

Claims 6-9 have been rejected under 35 U.S.C. § 102(e) as being unpatentable over U.S. Patent No. 5,436,154 ('154). Claim 7 has been cancelled.

The '154 patent discloses the use of anti-TNF antibodies in a method for treating or prophylaxis of the pathogenic effect of TNF in diseases which include myocardial ischaemia in a mammal. As discussed, for example, in column 1, the pathogenic effect is the inflammation response mediated by TNFα.

The methods of Claims 6 and 8-9, as amended, differ from the method of the '154 patent in the disorder to be treated (i.e., thrombosis versus the inflammatory response mediated by TNF during myocardial ischaemia). Therefore, Claims 6 and 8-9, as amended, are not anticipated by the '154 patent.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 102(e) are respectfully requested.

Rejection of Claims 6-8 Under 35 U.S.C. § 102(b)

Claims 6-8 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Squadrito *et al.* Claim 7 has been cancelled.

As with the above references, Squadrito *et al.* disclose, at best, a method of treating tissue injury (i.e., a myocardial

ischaemia-reperfusion injury) in a rat by administering antibodies raised against murine TNFα to the rat.

Therefore, for the reasons set forth above, Claims 6 and 8, as amended, are not anticipated by Squadrito *et al.*

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 102(b) are respectfully requested.

Rejection of Claims 9-15 Under 35 U.S.C. § 103(a)

Claims 9-15 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over either of U.S. Patent No. 5,436,154 ('154) or Squadrito *et al.* in view of WO92/16553. The Examiner states that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the A2 and cA2 antibodies, as taught in WO92/16553 in the treatment methods taught in either of Patent Number 5,436,154 and Squadrito *et al.*, which utilize antisera to tumor necrosis factor. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of WO92/16553; on the high binding affinity of the A2 antibody (see p. 9, line 29) and the usefulness of chimeric antibodies, such as cA2, in overcoming the "problems of murine antibody immunogenicity" and to "provide reduced immunogenicity and increased neutralization activity" (see p. 7, lines 14-17).

Applicants respectfully disagree with the Examiner's conclusion that the claimed invention was obvious.

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

Claims 9-15, as amended, relate to a method of treating or preventing thrombosis in an individual comprising administering a

chimeric anti-TNF antibody to the individual. Claims 10-15 further characterize the antibody.

U.S. Patent No. 5,436,154 discloses the use of anti-TNF antibodies in a method for treating or prophylaxis of the pathogenic effect of TNF in diseases which include myocardial ischaemia in a mammal.

Squadrito *et al.* disclose a method of treating a myocardial ischaemia-reperfusion injury in a rat by administering antibodies raised against murine TNFα to the rat.

WO92/16553 teaches both the A2 and cA2 antibodies, and antibodies which recognize an epitope containing amino acid residues 87-108 or 59-80 of hTNFα.

None of the cited references, nor their combination, teach or suggest the claimed methods of treating or preventing thrombosis in an individual. Furthermore, none of the cited references teach or suggest decreasing fibrinogen levels in a mammal, as claimed in Claims 29-50. Accordingly, a *prima facie* case of obviousness over the references of record has not been presented.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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